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The x-ray emission from a synchrotron provides the capability of obtaining high photon fluxes, selectable monoenergetic x-ray beams and a nearly ideal narrow beam geometry. Thus, the synchrotron provides the ideal x-ray imaging source to explore techniques for imaging soft tissues such as the breast. Under this grant we have developed a new imaging technique which we call Diffraction Enhanced x-ray Imaging (DEI). This technique has the potential to dramatically change mammography and radiography in general. Specifically developed as part of our x-ray mammography program utilizing monochromatic x-rays from a synchrotron source, this technique has produced images of test objects and tissue whose contrast and information content far exceeds conventional techniques. Preliminary work with human breast cancer specimens suggests that DEI images include information regarding specific physical characteristics of the lesion including border detail and associated features that are not detected by conventional imaging.

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Richard E. Johnston 7/21/98

PI - Signature Date

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2. INTRODUCTION

We are exploring the use of monoenergetic x-rays using both phantom objects and real tissue samples. We are experimentally comparing the synchrotron images to images obtained from conventional polyenergetic x-ray imaging systems. We are also developing a Monte Carlo simulation program designed to create accurate images simulating a full field digital mammography system (Fischer Senoscan) and the synchrotron imaging system with monoenergetic x-ray energies.

As a result of our exploration with monoenergetic x-rays, we have developed a new imaging technique which we have given the name Diffraction Enhanced Imaging. The new radiographic imaging method, Diffraction Enhanced Imaging, DEI, partly depends upon the refractive properties of an object in the creation of a scatter-free image. This new method, which seeks to improve the x-ray beam properties for improved contrast, along with the new digital mammography detectors could improve early detection of occult disease.

Background (exerpted from original proposal)

A small number of experimenters have explored the use of monoenergetic x-rays for medical imaging other than mammography [1,2,3]. Carroll, et.al.[4] have shown that there are significant differences in attenuation between normal and cancerous tissues for monoenergetic x-rays in the range of 14 to 18 keV. Boone and Seibert [5] did a computer simulation to compare performance of monoenergetic x-rays to polyenergetic x-rays from tungsten anode systems with regard to imaging. Their conclusion was that monoenergetic sources exhibited a 40 to 200 % improvement in tissue contrast when imaging the chest with different contrast targets. Admittedly, soft tissue contrast benefited the least. Burattini, et.al, [6,7] recently published their work using synchrotron radiation to image both breast phantoms and specimens. They conclude that the images obtained with monoenergetic x-rays have higher contrast, better resolution and similar, or less, radiation dose compared to the conventional polyenergetic x-ray images.

The following is a summary of our experience using a monoenergetic x-ray beam from the National Synchrotron Light Source (NSLS) at Brookhaven National Laboratory to explore the potential of monoenergetic photons for mammographic imaging.

Our preliminary experiments, [8] showed that we could obtain image contrast somewhat superior to that from conventional x-ray images, but due to instrumentation problems we had very noisy images. With improved instrumentation (scanning motor drive system, new monochromotor and clean beryllium windows on the beam port) we have been able to reduce the noise considerably. We have imaged various mammographic phantoms including the ACR, an anthropomorphic phantom, and a Contrast Detail phantom. We have also imaged a breast tissue sample. All of our experiments were carried out at energies from 16 keV to 24 keV.

More recently our research has centered on exploring DEI. Other researchers have applied diffractive optics to imaging problems[9-12] and have observed refraction effects. Also, there is great interest in phase contrast imaging which makes use of the high transverse coherence of third generation synchrotron sources. However, these types of measurements are limited to materially thin objects and/or high x-ray imaging energies

to obtain phase contrast images of the object[13-15]. The DEI technique works for thick samples and does not require the use of a synchrotron.

The mammography imaging technique which is under development utilizes the high intensity and collimation of synchrotron radiation to create a monoenergetic line scan imaging system which has very little scatter. One aspect of this program has been to study the use of an analyzer crystal as a scatter rejection optic. Experiments performed with this scatter rejection optic revealed that this imaging system is sensitive to refractive index effects within the object being imaged as well.

3. BODY

Methods:

The following is a description of the experimental methods used for our studies to explore the DEI technique of imaging. The experimental setup used to apply this technique is shown in figure 1 (see appendix 1) which shows both the synchrotron radiography system (figure 1a - upper figure) and the addition of the analyzer crystal to for the DEI system (figure 1b - lower figure) . The white synchrotron beam is made nearly monochromatic by a silicon double crystal monochromator. For the measurements described here the beam energy was either 18keV or 30keV. The pilot experiments were carried out at the National Synchrotron Light Source (Brookhaven National Laboratory, Upton, NY) using the X27C Research and Development Group beamline. Subsequent experiments were performed at the Advanced Photon Source (Argonne National Laboratory, Argonne, IL) using the Synchrotron Radiation Instrumentation Collaborative Access Team 1-BM beamline. The latest results are from a dedicated DEI facility being built on the X15A beamline at the National Synchrotron Light Source. The imaging beam was approximately 80 mm wide and 1 mm high at the location of the object. An ionization chamber was used to measure the radiation exposure at the surface of the object. Images taken with and without the analyzer were at exposure levels comparable to conventional mammography x-ray systems. The object to be imaged was mounted on a scanning stage that was driven by a stepping motor. The x-ray beam transmitted through the object could be either imaged directly as in normal radiography or following diffraction in the vertical plane by the silicon crystal analyzer. Radiation exposure to the image plate was controlled by adjusting the scan speed and absorbers in the incident beam to maintain an exposure of about 1.3•C/kg (5mR) to the plate. Typical scanning times for these experiments were on the order of 4 to 200 seconds. These limits were dictated by our scanning motors and mechanical system.

In acquiring the DEI apparent absorption and refraction images the phantom was exposed to approximately four times the exposure compared to the non-analyzer synchrotron radiographs. A factor of two in increased exposure compensates for the 0.5 reflectivity of the Bragg analyzer crystal and another factor of two increased exposure compensates for the two images on each side of the rocking curve.

The detector was a photo-stimulative phosphor image plate, typically used for radiology (Fuji Medical Systems high resolution HR5 and standard resolution ST5 image plates, Fuji Medical Systems USA, Stamford, CT). The image recorded on the plate was digitized, stored and displayed by a Fuji Medical Systems AC3 reader and workstation or

a BAS2000 reader system also manufactured by Fuji. The image plates were read out at 2560 x 2048 matrix size which results in an image resolution of 100 microns per pixel (0.1 x 0.1 mm2). The diffraction angle of the analyzer crystal could be finely tuned using a stepper-motor driven translation stage pushing on a long bar attached to an axle to which the crystal was attached (tangent arm). The resolution limit of the tangent arm was 0.1 microradian which was sufficient for placing the Bragg analyzer crystal at a selected position on its rocking curve.

For each sample, a "normal" radiograph with the monochromatic beam can be taken by moving the image plate to a location just downstream of the object on the sample scanning stage and scanning the combined object and image plate through the fan beam. DEI images were then acquired with the analyzer tuned to various positions on the rocking curve by translating the sample and the image plate in opposite directions at the same speed through the fan beam. The change in scanning direction arises from the beam inversion from the analyzer crystal. At a scan speed of about 10 mm/s, the surface dose on the sample was a few mGy at 18 keV and tenths of mGy at 30 keV. Rocking curves through a line on the phantom were obtained by fixing the phantom in the fan beam and performing a series of exposures by incrementally changing the analyzer position and image plate vertical position. The rocking curve is useful for quickly visualizing the optimum analyzer position for contrast enhancement of the desired features.

Results:

Phantom studies:

The standard phantom used for quality control in mammography is the American College of Radiology (ACR) phantom. It contains features which simulate lesions commonly found in breast tissue, namely tumor-like masses (lens-shaped objects of different thickness' and diameters), simulated micro-calcifications arranged as vertices of five-point stars and cylindrical nylon fibrils [12]. A schematic of this test object is shown in figure 2a. This phantom approximates a 40 to 45 mm thick compressed breast. Figure 2b is a conventional radiograph of the ACR phantom. Figure 2c is a DEI image taken with the analyzer set 3 microradians from the peaked position. Note that all the features of the phantom are visible in the image as well as some tape used to hold the phantom to a Lucite holder. Also note that the tumor simulations have excess intensity compared to the surrounding area. This is a result of the analyzer diffracting the small angle scattering from the simulations at the 3 microradian offset angle. The tumor simulation in the upper right hand corner has a contrast enhancement of a factor of 27 due to rejection of small angle scattering.

Excised Human Tissue Results:

A total of 7 formalin-preserved human breast cancer specimens were imaged, including samples containing infiltrating ductal carcinomas. Each biological sample was sealed in a plastic bag and compressed between two Lucite plates. Lucite plates were added during the imaging to make the absorbing thickness on the order of 40 mm.

Images of a breast tissue acquired at 18 keV are shown in Fig.3. Fig.3a shows a "normal" specimen radiograph taken with a Fischer full-field digital mammography unit.

Figures 3b and 3c show the apparent absorption and refraction images, respectively, of the sample. These images are derived from the images taken at ± 1.5 microradians on each side of the analyzer rocking curve. Compared to the "normal" radiographs, the apparent absorption image (Fig.3b) shows more contrast for the tumor compared to the background normal breast tissue. The DEI apparent absorption image also shows the calcifications (clusters of white dots in the image) better than normal radiography. The most striking feature is the visualization of small spiculations which are only poorly seen in the conventional image. This is indicated in the circled regions. These "bands" are comprised of fibrous tissue and are seen radiating from the periphery of the carcinoma on the pathology slide, figure 3d. This is a reaction of the normal breast to the presence of carinoma and may be the first sign detected by the radiologist.

After the DEI images were obtained, the specimens were evaluated by an expert breast pathologist (JG) and an expert breast imaging radiologist (EDP) using histologic whole-mounts slides. The study of these specimens was performed in order to confirm that the increased detail apparent in the DEI images (both in the apparent absorption images and the diffraction images) correlates with real histologic-anatomic structures.

In general terms, the DEI images have shown improved visualization of calcifications (in 6/7 cases) and spiculations (or architectural distortion) (in 7/7 cases). These are mammographic features that aid radiologists in detection and classification of breast lesions. As is seen in the accompanying illustrations, this improved detail has been confirmed as representing real histologic-anatomic structures. For example, spiculations that are better visualized with the DEI method correlated with structures seen on the histologic slides by the pathologist, sometimes representing breast cancer itself extending into the surrounding breast tissue, and sometimes representing fibrosis (scarring), the breast's natural reaction to the tumor's presence. In no instance has the increased lesion detail present in the DEI images proven to be artifactual. The accompanying illustrations show the improved visualization of spiculations representing tumor extension, spiculations representing fibrosis, and calcifications seen within the DEI image that were visualized within the pathologic specimens but that could not be seen on the conventional radiographs. Clearly, this amount of improved detail is quite promising, especially when one considers the fact that we have not yet optimized this technique for breast imaging.

Monte Carlo Simulations:

In the past year a great deal of progress has been made in the Monte Carlo modeling of the synchrotron imaging concept. The first step was the measurement of the coherent scattering form factors for tissue. These data are required to model the images correctly and make an accurate assessment of the scattered radiation contribution to the image. The measurements were done at the National Synchrotron Light Source, Brookhaven National Laboratory. Fresh bovine and swine tissue samples were measured -- including muscle, adipose, kidney, liver and blood. Breast tissue in formaline and plastics commonly used in mammographic phantoms were also measured. Two examples are shown in Figure 4 (see appendix).

Slight differences were seen between tissue types and a large difference was seen between tissues and adipose. A paper describing the measurement method and listing the molecular coherent form factor for each sample has been accepted for publication by

Physics in Medicine and Biology. Researchers in other fields should also benefit from the extensive data collected on the various tissues types.

A unique approach to simulating images by the Monte Carlo method was developed and will be presented this November at the American Nuclear Society winter meeting. By calculating the unscattered and scattered image components separately on different mesh sizes and then adding them together later, full field mammographic images using realistic pixel sizes can be simulated in reasonable amounts of time. Measurements of mammographic phantoms were taken at the NSLS for comparison with the results of our Monte Carlo code. Comparisons of Monte Carlo and real images are shown in Figures 5 and 6. Analysis of the contrast of the objects in the contrast detail phantom images show very good agreement between Monte Carlo and the synchrotron images.

The concept of splitting the simulation into the unscattered and scattered components is a new idea in image simulation. In fact, realistic image simulation is not done very often due to the extraordinarily large times needed. With this new concept, image simulation in many areas of medical physics will be possible in reasonable times.

4. CONCLUSIONS

During this second year we have explored the use of monoenergetic x-rays to image samples of real breast tissue comparing DEI, monoenergetic radiographs and conventional mammography. We have demonstrated that the DEI images show structures in better detail than seen with conventional x-ray image systems, and in some cases show detail that was not visualized with the conventional system.

The Monte Carlo simulation program we have developed is a powerful tool which can be used to determine the sensitivity of the imaging system to various parameters, such as beam energy or tumor density. This work is being extended under a DOE NEER grant to determine The optimum parameters for the synchrotron imaging system. Comparisons to conventional digital imaging (with a tube anode) will also be carried out using Monte Carlo simulation. Eventually, differential sampling will be added to the code.

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7.NSLS Activity Report. An abstract of the form factor measurement work was published in the 1997 Activity Report of the National Synchrotron Light Source.

APPENDIX 1: FIGURES

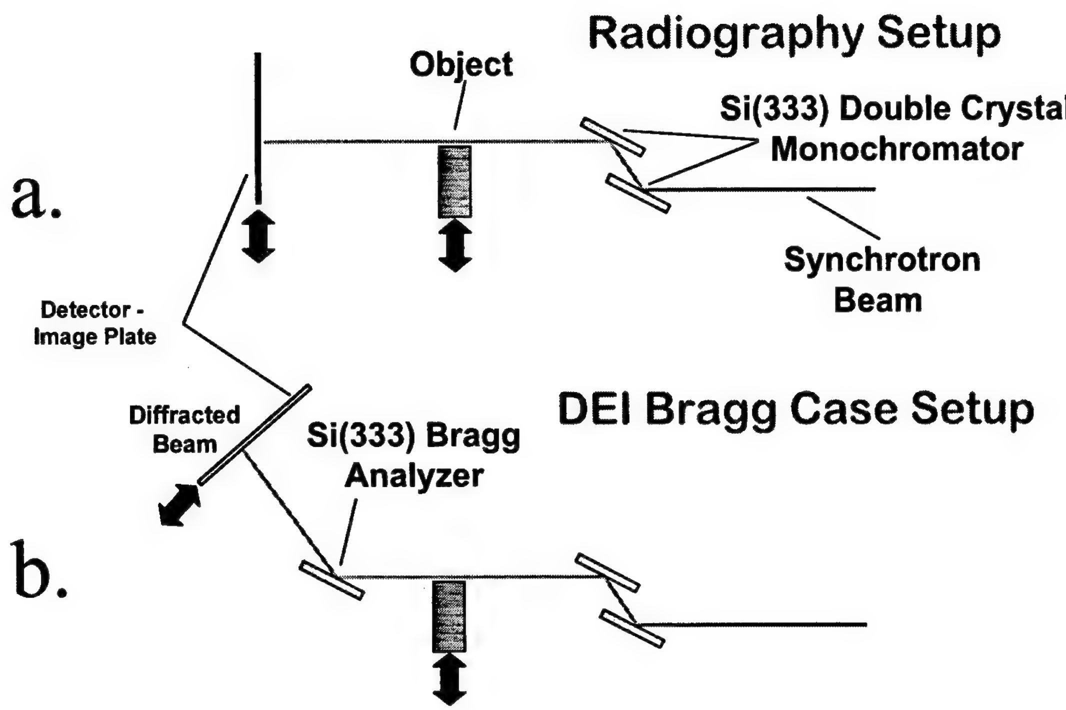
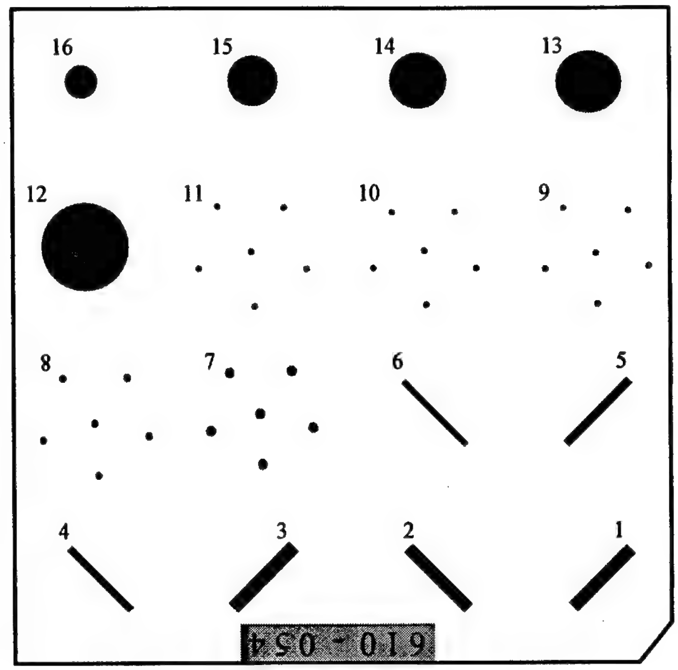


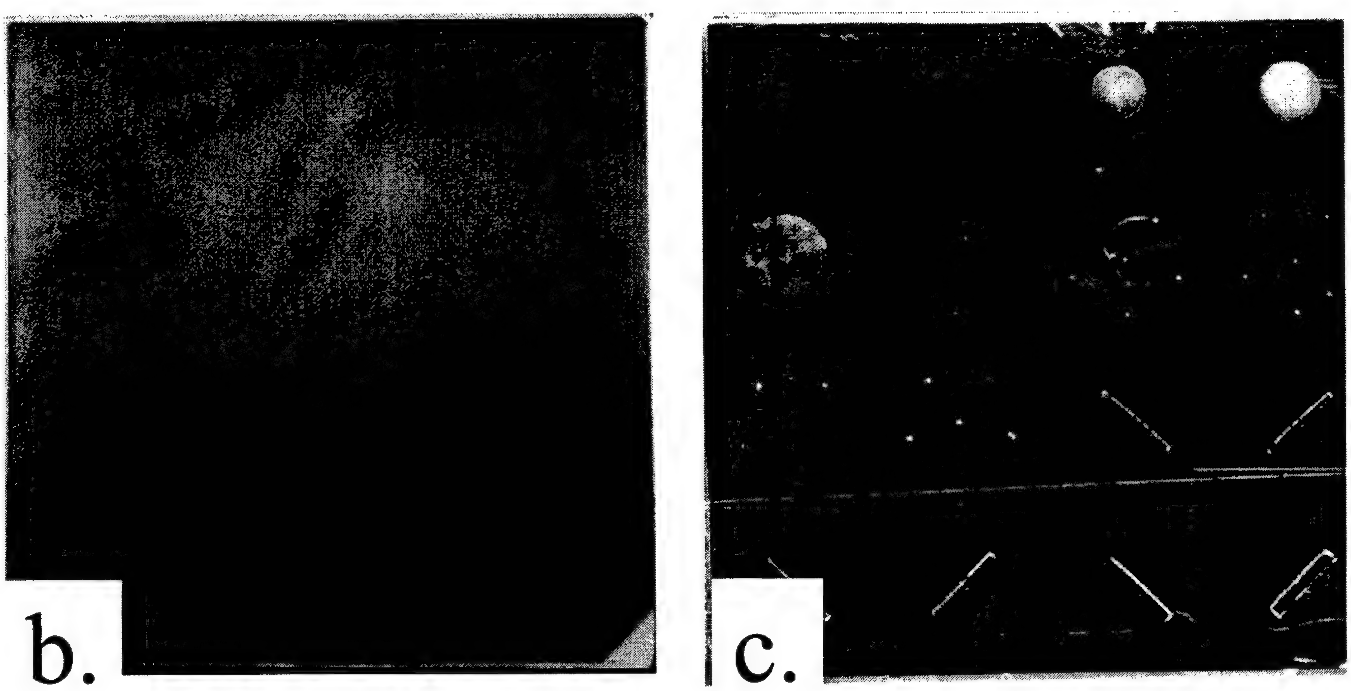
Figure 1. Experimental Setup. Figure 1a schematically shows the synchrotron setup used to obtain radiographs of the object. Figure 1b shows the addition of the analyzer crystal (Bragg or reflection geometry) used to implement the DEI system.

Region Materials

1. 1.56 mm nylon fiber
2. 1.12 mm nylon fiber
3. 0.89 mm nylon fiber
4. 0.75 mm nylon fiber
5. 0.54 mm nylon fiber
6. 0.40 mm nylon fiber
7. 0.54 mm simulation micro-calcification
8. 0.40 mm simulated micro-calcification
9. 0.32 mm simulated micro-calcification
10. 0.24 mm simulated micro-calcification
11. 0.16 mm simulated micro-calcification
12. 2.00 mm tumor-like mass
13. 1.00 mm tumor-like mass
14. 0.75 mm tumor-like mass
15. 0.50 mm tumor-like mass
16. 0.25 mm tumor-like mass



a.



b.

c.

Figure 2. The American College of Radiology quality assurance phantom for mammography. Figure a is a schematic of the phantom with each feature identified. Figure b is a conventional radiograph of this phantom taken with a Siemen's Mammomat II system. Figure c is a DEI image taken at 18keV with the analyzer in place and at 3 microradians from the peak position.

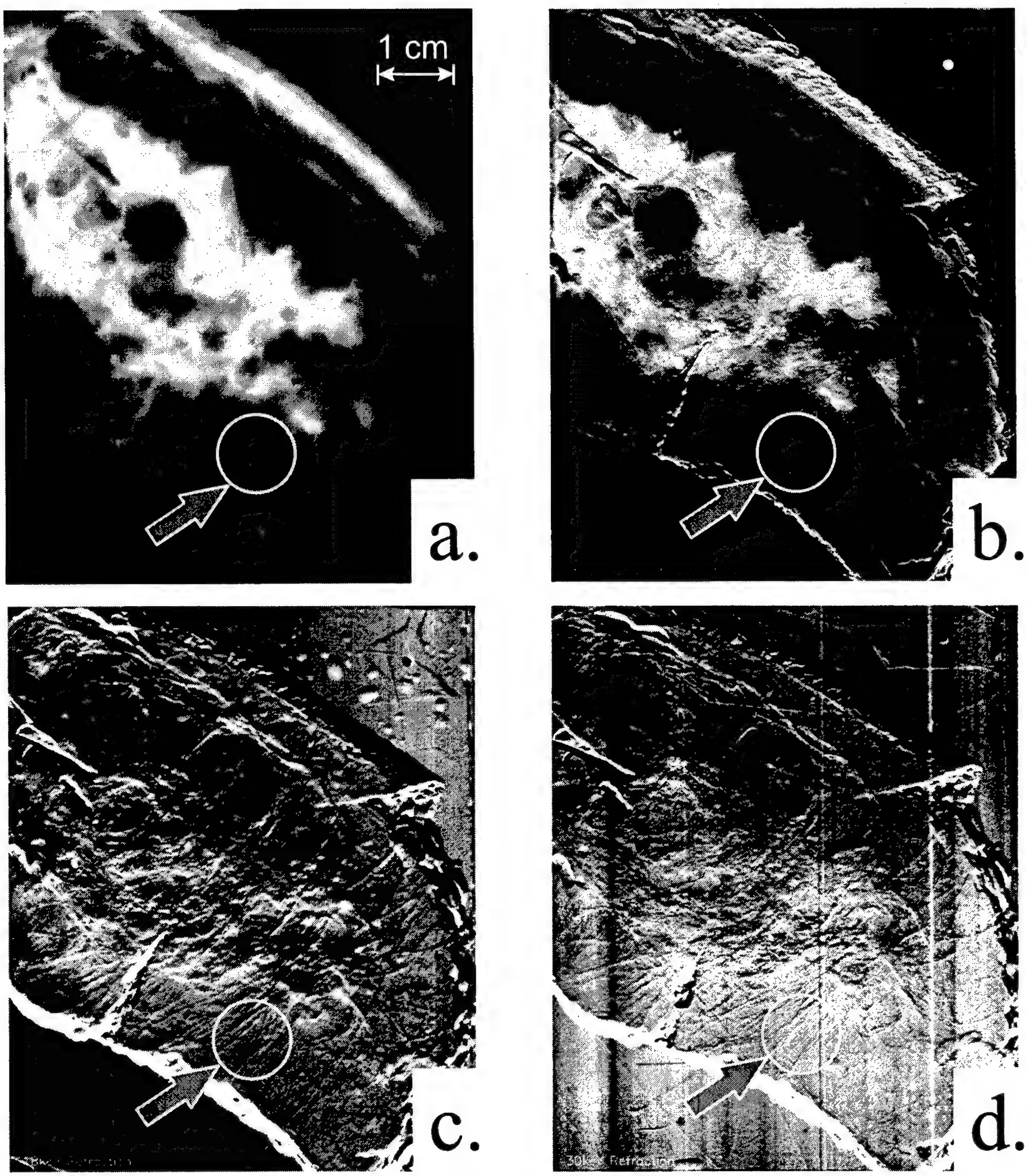
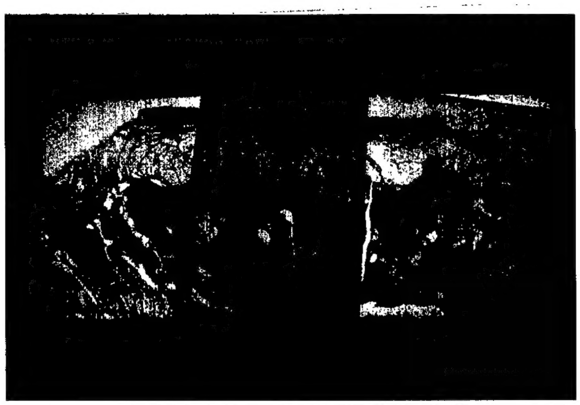


Figure 3. Images taken of an excised breast tissue sample with infiltrating ductal carcinoma. Figure a shows an image taken of this sample with a Fischer digital mammography unit at University of North Carolina. Figure b shows the DEI apparent absorption image and c shows the refraction image. Figure d show a DEI refraction image taken at 30keV. The circled regions indicate refraction from spiculations (figs. c and d) which is not readily apparent in the radiograph or apparent absorption images (figs. a and b).



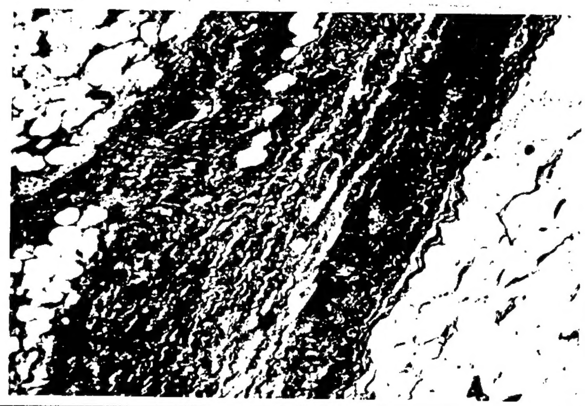


Figure 3 e Histologic Whole-mount **Figure 3 f Photomicrograph**

Figure e and f show that these bands are comprised of fibrous tissue and are seen radiating from the periphery of the carcinoma This is a reaction of the normal breast tissue to the presence of carcinoma and may be the first sign detected by the radiologist.

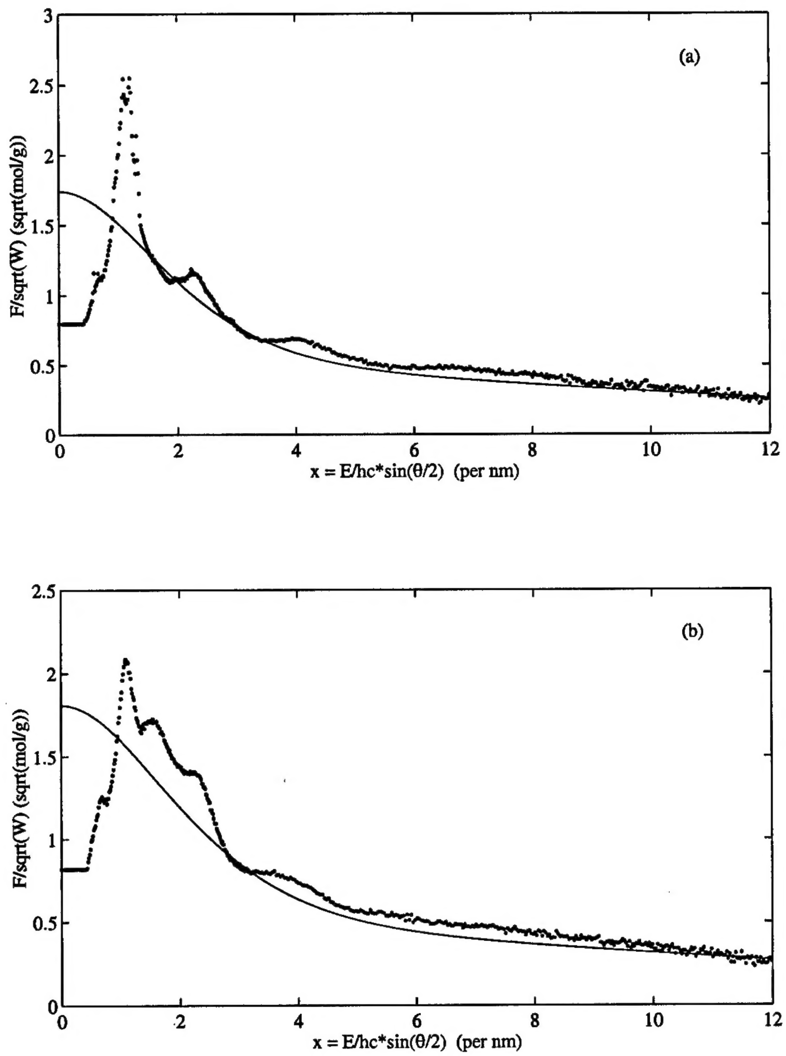


Figure 4: Molecular coherent scattering form factors of (a) pork fat and (b) human breast tissue. The free-gas theory is shown as the solid line and the measured form factors are shown as points. The large differences at lower x values is the reason for having to measure the form factors.

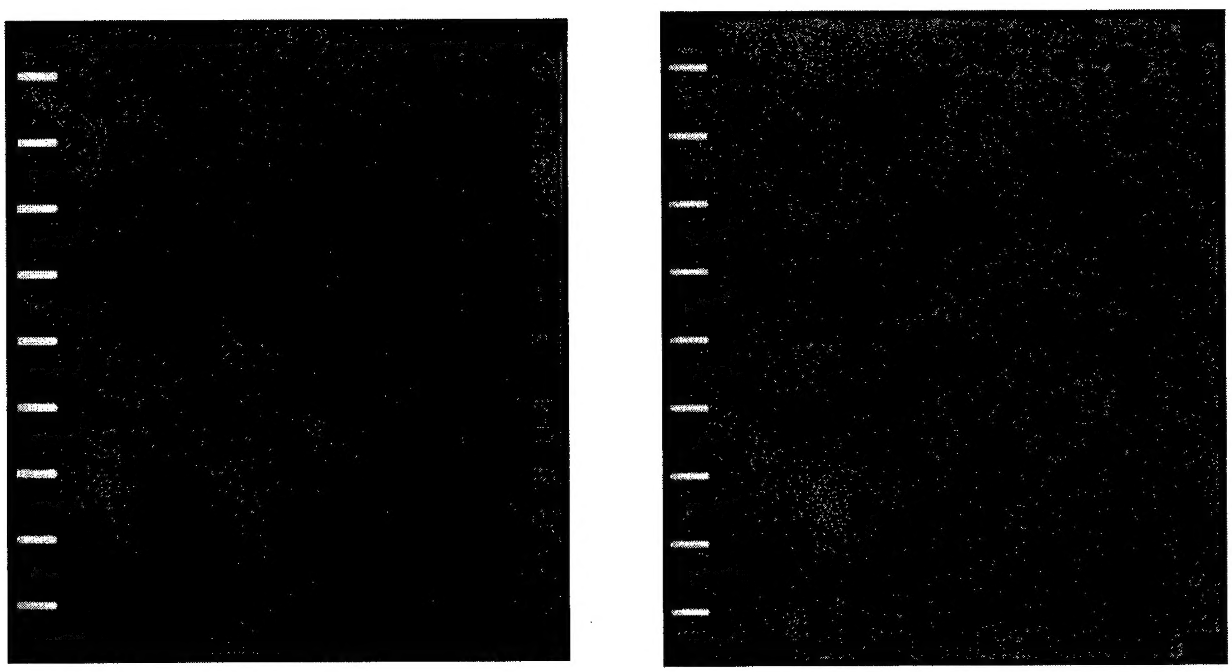


Figure 5: Images of the contrast detail phantom. Left-image taken with synchrotron radiation. Right-simulation by Monte Carlo. The actual images contain artifacts from the image plate, image reader and x-ray optics.

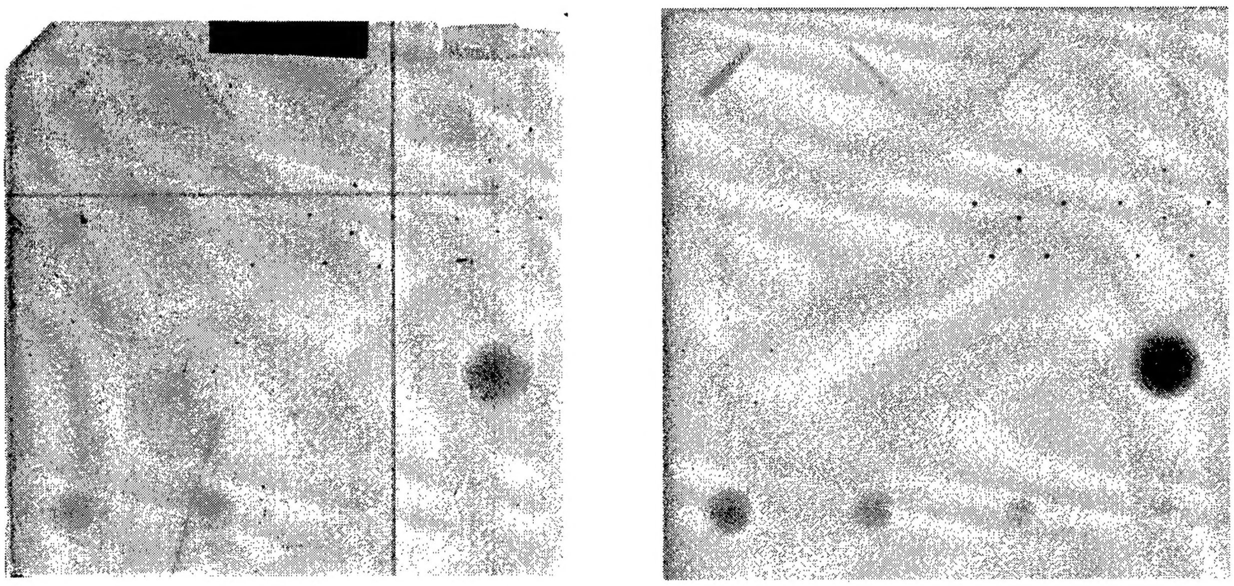


Figure 6: Images of the ACR phantom. Left-image taken with synchrotron radiation. Right-simulation by Monte Carlo. The manufacturer of the ACR phantom acknowledges that there is some variability around the technical standards used in the Monte Carlo.